Table WEB-1: Summary of DINP General Toxicity Studies in Rats

Strain	Experimental Regimen	Number/ Sex	Dose (mg/kg/day)	Body Weight	Organ Weight*	Liver Effects	Hematology	Other
Fischer 344 Bibra et al. 1985	Subchronic study – 21 days. Rats (~41–43 days old) were fed diets with 0, 0.6, 1.2, or 2.5% DINP and then sacrificed and necropsied. Peroxisomal proliferation was studied by electron microscopy examination of liver and measurement of peroxisomal enzyme activity.	5	0					
		5	639(M)/ 607(F)	NE	↑Li, Ki	↑11-OH and 12-OH(M) ↑Protein	NA	↓Serum Ch, Tg(M)
		5	1,192(M)/ 1,193(F)	↓	↑Li, Ki	↑PCAO, 11-OH and 12-OH(M) ↑Protein Histological changes	NA	↓Serum Ch, Tg(M) ↑Serum Tg(F)
		5	2,195(M)/ 2,289(F)	↓	↑Li, Ki, Te	↑PCAO, 11-OH and 12-OH ↑Peroxisomes ↑Protein Histological changes	NA	↓Serum Ch, Tg(M) ↑Serum Tg(F) No testicular lesions
	↑A group of positive control rats was administered DEHP.	*5*	*1,084(M)/ 1,063(F)*	*↓(F)*	*↑Li, Ki*	*↑PCAO, 11-OH and 12-OH* *↑Peroxisomes* *↑Protein*	*↑NA*	*↓Serum Ch, Tg(M)* *No testicular lesions*

*Organ to body weight ratio
NA=Not analyzed
NE=No effects
F=Female
M=Male
↑= Statistically significant increase
↓=Statistically significant decrease
Te=Testes
PCAO=Palmitoyl-CoA Oxidase
Tg=Triglyceride
Ch=Cholesterol
Li=Liver
Ki=Kidney
11-OH=11-Hydroxylase
12-OH=12-Hydroxylase
PCAO=Palmitoyl-CoA Oxidase

Table WEB-2: Summary of DINP General Toxicity Studies in Rats

Strain	Experimental Regimen	Number/ Sex	Dose (mg/kg/day)	Body Weight	Organ Weight	Liver Effects	Hematology	Other
Fischer 344 Lington et al. 1997	Chronic study – 2 years. Six-week-old rats were fed diets with 0, 0.03, 0.3, and 0.6% DINP-1 for 2 years. Ten rats/sex/group were sacrificed and necropsied at 6, 12, and 18 months and the rest were killed and necropsied at the end of the study. Hematology, serum chemistry, and urinalysis were evaluated every 6 months. Peroxisome proliferation was examined microscopically in 2 rats/sex/group at 24 months.	110 110 110 110	0 15(M)-18(F) 152(M)-184(F) 307(M)-375(F)	NE ↓(M; 18–24 mo) ↓(M; 12–24 mo)	NE ↑Li, Ki (6–24 mo) ↑Li, Ki (6–24 mo) ↑Sp (24 mo) ↑Ad (24mo)	NE Hepatocyte enlargement (6–24 mo) and lesions (24 mo) ↑SGOT (M; 6–12 mo), SGPT (M; 24 mo) ↑MNCL Hepatocyte enlargement (6–24 mo) and lesions (24 mo) ↑SGOT (M; 6–18 mo), SGPT(M; 6 and 18 mo) ↑MNCL No evidence of peroxisomal proliferation	NE NE ↓RBC, Hg, Hc (M; 24 mo)	NOAEL ↓Survival (F) ↓Survival (F) ↑ Urine volume (M; 6–24 mo) ↑ Urine K and glucose (M; 6–18 mo) No evidence of testicular damage

NA=Not analyzed
NE=No effects
↑= Statistically significant increase
↓=Statistically significant decrease
M=Male
F=Female
Li=Liver
Ki=Kidney
Sp=Spleen
RBC=Red Blood Cell
Hg=Hemoglobin
Hc=Hematocrit
Ad=Adrenal
SGOT=Serum Glutamic Oxaloacetic Transaminase
SGPT=Serum Glutamic Pyruvic Transaminase
MNCL=Mononuclear Cell Leukemia
Mo=Months
K=Potassium

Table WEB-3: Summary of DINP General Toxicity Studies in Rats

Strain	Experimental Regimen	Number/Sex	Dose (mg/kg/day)	Body Weight	Organ Weight*	Liver Effects	Hematology	Other
F344 Rats Moore 1998	Chronic study – 2 years. Six-week old rats were fed diets with 0, 500, 1500, 6000, or 12,000 DINP. Five rats/sex/dose were killed on weeks 1,2, and 13; 15 rats/sex/dose were killed at 79 weeks; and 55 rats/sex/group at 104–106 weeks. Clinical evaluations (hematology, serum chemistry, and urinalysis) were conducted every 26 weeks. Peroxisome proliferation was examined in 5 rats/sex only the controls and highest dose group during weeks 1, 2, and 13 and in 3–5 rat/sex in controls, 359–442 mg/kg/day group, and high dose group at week 104.	85 70 70 85 85	0 29.2(M)/ 36.4(F) 88.3(M)/ 109(F) 359(M)/ 442(F) 733(M)/ 885(F)	NE NE NE ↓ (wk 9–104)	NE NE ↑Ki(wk 79–104) ↑Li (wk 1–104) ↑Ki (wk 79–104), Li (wk 1–104)	NE NE ↑PCAO (F, wk 104) ↑AST, ALT (wk 52, 78, 104) ↑PCAO (wk 1–104) Lesions (wk 2–104) Neoplasia (M, wk 79–104) ↑AST, ALT (wk 52, 78, 104) ↓AST, ALT (F, wk 26)	NE NE ↑Anemia ↑Anemia	NE NOAEL Kidney lesions (M, wk 79–104) ↑ Serum urea (wk 26–104) MNCL (wk 104) ↓Survival (M) ↑Serum urea (wk 26–104) ↑Urine vol with ↓Cl, Ca, K and cre(M, wk 104) Kidney lesions (wk 79–104) Kidney neoplasm (M, wk 104) MNCL (wk 104) No testicular effects
	A group of 55 rats/sex was exposed to the high dose for 78 weeks and sacrificed at 105–106 weeks to study recovery effects.**	55	637(M)/ 774(F)	↓(F)	↑Ki(F)		NE	↑Urine vol with ↓ cre(M) MNCL (wk 104) Kidney lesions and neoplasm (M)

* Organ to body weight ratio

**Only effects observed by week 104 were listed.

NA=Not analyzed
NE=No effects
↑= Statistically significant increase
↓=Statistically significant decrease
M=Male
F=Female
Li=Liver
Ki=Kidney
K=Potassium
Cre=Creatinine
PCAO=Palmitoyl-CoA Oxidase
Cl=Choride
Ca=Calcium
Wk=Week
AST=Aspartate aminotransferase
ALT=Alanine aminotransferase
MNCL=Mononuclear Cell Leukemia
Vol=Volume

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Table WEB-4: Summary of DINP General Toxicity Studies in Mice

Strain	Experimental Regimen	Number/ Sex	Dose (mg/kg/day)	Body Weight	Organ Weight*	Liver Effects	Hematology	Other
B6C3F1/ CrlBR mice Moore 1998	Chronic study – 2 years. Six-week old mice were fed diets with 0, 500, 1500, 4000, and 8000 ppm DINP. Fifteen mice/dose/sex were evaluated and sacrificed at 79 weeks and 55 mice sex/group at 105–106 weeks. Clinical evaluations (hematology, serum chemistry, and urinalysis) were conducted every 26 weeks. Peroxisome proliferation was examined in 5 mice/sex in the highest dose group and controls during the midpoint and end of study.	70	0					
		70	90.3(M)/ 112(F)	NE	NE	NE	NE	NOAEL (F)
		70	276(M)/ 336(F)	NE	NE	↑Neoplasia (F)	NE	NOAEL (M)
		70	742(M)/ 910(F)	↓ (week 1–104)	↓Ki(M), ↑Li(M) (week 79–104)	↑Neoplasia (M)	NE	NE
		70	1,560(M)/ 1,888(F)	↓ (week 1–104)	↓Ki (M), ↑Li (week 79–104)	↑Neoplasia and non-neoplastic changes ↑Serum AST, ALT (M) ↑PCAO (week 79–104)	↓WBC (week 26–98)	↓Survival (M) ↑Nephropathy(F) ↑Serum protein (M, week 104) ↑Urinary vol. with ↓Na, Cl, K (week 52–104) No effects on testicular histology
	A group of 55 mice/sex was exposed to the high dose for 78 weeks and sacrificed at 105–106 weeks to study recovery effects.**	55	1,377(M)/ 1,581(F)	↓(M)	↓Ki(M)	↑Neoplasia	NE	NE

* Organ to body weight ratio

**Only effects observed by week 104 were listed.

NA=Not analyzed
NE=No effects
↑= Statistically significant increase
↓=Statistically significant decrease
M=Male
F=Female
Li=Liver
Ki=Kidney
WBC=White Blood Cell
Ep=Epididymous
Te=Testes
PCAO=Palmitoyl-CoA Oxidase
Trans=transient
Cre=Creatinine
Na=Sodium
Cl=Choride
K=Potassium
AST=Aspartate Amino Transferase
ALT=Alanine Amino Transferase
Vol=volume

Table WEB-5: Summary of DINP General Toxicity Studies

Strain	Experimental Regimen	Number /Sex	Dose (mg/kg/day)	Body Weight	Organ Weight	Histopathology	Hematology	Chemistry	Other
Marmoset Hall et al. 1999	Subchronic study – 13 Weeks. Male and female marmosets (16–25 months old) were gavaged with DINP in 1% methylcellulose and 0.5% Tween. Clofibrate was used as a positive control. Parameters evaluated at sacrifice included estradiol and testosterone concentrations, biochemical evidence of peroxisomal proliferation, and organ weights and histopathology.	1–2 2 2 2 *1–2*	0 100 500 2500 *500 Clofibrate*	NE NE ↓[a] ¯[a]	NE NE NE - *Ki/bw*[a]	NE NE NE *NE*	NE NE NE ↑ *Anemia*	NE NE [*]No change in PCAO ↑ *PCAO* ↑*11-OH*	Ungroomed coat and reddening of the skin. Thin appearance, hunched posture and reduced activity in one male.[a]

[a] Effects were not statistically significant
*Was deleted in summary

NA=Not analyzed
NE=No Effects
M=Male
F=Female
Ki/bw=Kidney to body weight ratio
↑11-OH = Lauric acid 11-hydroxylase activity
↑12-OH = Lauric acid 12-hydroxylase activity
PCAO=Palmitoyl-CoA Oxidase activity

Table WEB-6: Summary of Diisononyl Phthalate (DINP) Developmental Toxicity Studies in Rats

Strain	Experimental Regimen	Number[b]	Dose (mg DINP/kg bw/day)	Effects	
				Maternal	Fetal
Wistar Rat Hellwig et al. et al. 1997	Prenatal developmental toxicity study. Three types of DINP[a] manufactured by different processes were administered in oil by gavage on gd 6–15. Dams were weighed on gd 0, 6, 10, 15, and 20 and Sacrificed on gd 20. Maternal uteri were weighed, corpora lutea were counted and implantation sites examined. Fetuses were weighed and examined for gross external malformations. Half the fetuses were examined for visceral malformations and the other half for skeletal malformations.	9 9–10 8–10 9–10	0 40 200 1,000	 ↑Kidney to bodyweight ratio in DINP-2 ↓Implantation sites/litter in DINP-2 No effects ↑Kidney to bodyweight ratio in DINP-1 ↑Liver to bodyweight ratio in DINP-3	 ↓Live fetuses/litter in DINP-2 No effects ↑Fetuses/litter with cervical ribs in: DINP-1: 11 fetuses in 5 litters vs 0 fetuses DINP-2: 4 fetuses in 4 litters vs 0 fetuses DINP-3: 12 fetuses in 7 litters vs 0 fetuses ↑Fetuses/litter with lumbar ribs in: DINP-1: 37 fetuses in 10 litters vs 0 fetuses DINP-2: 10 fetuses in 5 litters vs 0 fetuses DINP-3: 34 fetuses in 8 litters vs 0 fetuses ↑Fetuses/litter with hydroureter in DINP 3: 12 fetuses in 8 litters vs 4 fetuses in 3 litters ↑Fetuses/litter with malformations in DINP-3 (7.3 vs 4.3%)[c]

[a](1) CAS: 68515-48-0; (2) CAS: 28553-12-0; (3) CAS: 28553-12-0 by different manufacturing process
[b] Number of litters examined per type of DINP
[c] Skeletal and visceral malformations (humorous, femur, kidney, and ureter); Not statistically significant

Table WEB-7: Summary of Diisononyl Phthalate (DINP) Developmental Toxicity Studies in Rats

				Effects	
Strain	*Experimental Regimen*	*Number*	*Dose (mg DINP/kg bw/day)*	*Maternal*	*Fetal*
Sprague-Dawley Rat Waterman et al. et al. 1999	Prenatal developmental toxicity study. DINP-1 administered in oil by gavage on gd 6–15. Sacrificed on gd 21. Dams weighed on gd 0, 6, 9, 12, 15, 18, and 21. Maternal uterus and ovaries were weighed, corpora lutea were counted and implantation sites examined. Fetuses were weighed, sexed, and examined for gross external malformations. Half of fetuses were examined for visceral malformations and the other half for skeletal malformations.	24	0		
		25	100	No effects	↑ % Fetuses with dilated renal pelves (3.7 vs 0%)
		24	500	Maternal NOAEL	↑ % Fetuses with dilated renal pelves (4 vs 0%) ↑ % Fetuses with lumbar ribs (19 vs 4%)
		23	1,000	↓ Weight gain (transient) ↓ Food intake (transient)	↑% Litters with dilated renal pelves (26 vs 0%) ↑ % Fetuses with dilated renal pelves (4.5 vs 0%) ↑ % Litters with lumbar ribs (78 vs 25%) ↑ % Fetuses with lumbar ribs (35 vs 4%) ↑ % Fetuses with cervical ribs (6 vs 2%)

Table WEB-8: Summary of Di-isononly phthalate (DINP) Reproductive Toxicity Studies in Rats

Strain	*Experimental Regimen*	*Number/ Sex*	*Dose* (mg DBP/kg bw/day)*	*Effects*
CD Rats (Waterman et al. in press)	Two generation reproductive toxicity study. DINP administered in feed for 10 weeks prior to mating. Males treated until delivery of last litter and females through gestation to lactation. Breeding pairs housed together for 3 weeks; body weight and food intake was measured weekly, One male and female from each litter reared to adulthood and remaining pups were examined and discarded.	30	0	
		30	~250	↑Kidney weight in F_0 females ↓Weight gain in F_1 pups
		30	~290	↑Liver weight in F_0 females ↑Kidney weight in F_0 males and females ↓Weight gain in F_1 pups
		30	~500	↓Weight gain in F_0 females (pnd 14, 21) ↑Liver weight in F_0 males and females ↑Kidney weight in F_0 males and females ↓Left ovary weight in F_0 ↓Weight gain in F_1 pups No effect on weights of male reproductive organs, testicular histology, or litter size, mating, offspring survival, and sex ratio.
	One male and female F_1 rat/litter continued to receive the same doses as parental rats and was then mated within dose groups during adulthood.		0	
		30	~250	No effects
		30	~290	↓F_2 pup weight gain during lactation
		30	~500	↓Body weight in F_1 ↑Liver weight in F_1 females and kidney weight in F_1 males ↓F_2 pup weight gain during lactation No effects on mating, fertility, litter size, pup weight, survival, or sex ratio, sex organ weights or testicular histology.

*Dose calculations were unconventional